

IN 99/55

REC'D 12 JAN 2000

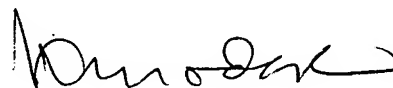
WIPO PCT

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THE PATENTS ACT, 1970#2
10/031854**PRIORITY DOCUMENT**SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

IT IS HEREBY CERTIFIED that annexed hereto is a true copy of the Application form and Complete Patent Specification in respect of Patent Application No.661/Cal/99 filed on 26th July, 1999 by RAJGARHIA, Ashok, C/o. Rajgarhia Paper Mills Pvt. Ltd., 15, Exchange Place, Calcutta 700 001, India.

Witness my hand: This the 25th day of October, 1999
This the 3rd day of Kartika 1921 (Saka)



(K. K. MODAK)
ASSTT. CONTROLLER OF PATENTS & DESIGNS

The Patent Office,
Government of India,
2nd M.S.O. Building, 5th 6th & 7th floor,
Nizam Palace,
234/4, Acharya Jagadish Chandra Bose Road,
Calcutta 700 020.

FORM 1
THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
(See Sections 5(2), 7, 54 and 135)

1. I/we,

(a) *RAJGARHLA, Ashok*

(b) C/o Rajgarhia Paper Mills Pvt. Ltd., 15 Exchange Place, Calcutta - 700001, India.

(c) Indian

2. hereby declare -

(a) that I am/we are in possession of an invention titled "*A Synergistic Composition For The Treatment Of Liver And Liver Associated Ailments.*"

(b) that the provisional/ complete specification relating to this invention is filed with this application

(c) that there is no lawful ground of objection to the grant of a patent to me/us.

3. further declare that the inventor(s) for the said invention

4. I/we claim the priority from the application(s) filed in convection countries, particulars of which are as follows: *NIL*

5. I/we state that the said invention is an improvement in or modification of the invention the particulars of which are as follows and of which I/we are the applicant/patentee: *NIL*

6. I/we state that the application is divided out of my/our application, the particulars of which are given below and pray that this application be deemed to have been filed on under section 16 of the Act. *NIL*

7. That I am/we are the assignee or legal representative of the true and first inventors

29 SEP 1999

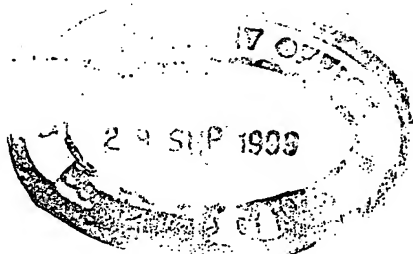
I/we request that a patent may be granted to me/us for the said invention

Dated this 21st day of July, 1999

M. R. R. R.

RAJGARHIA, Ashok

To
The Controller of Patents
The Patent Office,
Calcutta



THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

SECTION 10

*" A SYNERGISTIC COMPOSITION FOR THE TREATMENT OF
LIVER AND LIVER ASSOCIATED AILMENTS "*

*Ashok Rajargarhia, an Indian national of Rajargarhia Paper Mills Pvt.
Limited, 15 Exchange Place, Calcutta 700001, West Bengal, India*

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a synergistic composition for the treatment of liver and liver associated ailments.

Background

Liver is an important organ in the human body and is responsible for its well being. It helps in detoxifying many exogenous toxic substances present within the human body, which are consumed as drugs or with food. These toxic wastes reduce the efficiency of the liver as a blood purifier. Liver also undergoes frequent attacks by viral infections such as hepatitis.

India has the second largest pool of HBV carriers in the world. It has a population of over 45 million HBV carriers and 15 million HCV carriers. One fourth of these are at risk to suffer from chronic liver diseases and its lethal complications, such as cirrhosis or even liver carcinoma. Coupled with the burden of HBV related liver diseases, there is an ever increasing patient load due to Hepatitis C. Screening of all the blood before use for HIV, is still a distant reality and this contributes to a significant increase in chronic liver diseases in India.

Therefore it has become absolutely essential to develop an effective therapeutic strategy to tackle this problem.

In allopathy, at present no specific drug is available for providing adequate cover for protection of or preventing liver from various infections and diseases. In Ayurveda, many plant extracts are known, which have a hepatoprotective effect. However, the effect of such crude plant extracts as used in Ayurveda is slow by virtue of presence of other components which may prevent full action of the active ingredient/component.

One of the plant extracts used as medicine for treatment of liver diseases is the root extract of plant *Glycyrrhiza glabra* (liquorice).

Said extract contains flavonoids, saponins, oligo-glycosides, phenolic compounds and glycyrrhizic acid. Glycyrrhiza glabra is known to have four actions which help in treatment and prevention of liver diseases (Sub acute liver failure, cirrhosis liver with activity)

Cyto-protective action - This helps in fortifying the cell, which enables the cell to protect itself from virus / infection.

Anti-inflammatory and Immunomodulatory action - This helps in reducing the inflammation of the organ and help modulate the organ to function normally. It also has cholerectic action.

Anti-oxidant action - Helps in preventing replication of virus.

Anti-viral action - The combined effect of the above helps in preventing replication of virus, thus there is reduction of viral load over a period of continued administration of the drug.

The activity of the extract of Glycyrrhiza glabra is also due to the action of beta glycyrrhizinic acid at the level of complement component C2.

However, liquorice extract when taken in large quantities for prolonged periods, causes high blood pressure (hypertension), water retention, weight gain due to pseudoaldosteronism and possibly heart complications.

Extract of roots of Picrorrhiza Kurroa have also been recommended as a hepatoprotective agent for protection of liver toxicity caused by hepatotoxic agents such as alcohol, carbon tetra chloride, viruses and parasites. Roots of Picrorrhiza kurroa contain glycosides, kutkin (kutkosides and picrosides) and other organic acids such as vallanic and cinnamic acids.

The extract of Picrorrhiza roots is bitter and it increases gastric secretion, diminishes the force of heartbeat and reduces the blood pressure.

Therefore there was a need to develop a synergistic composition having a pleasant flavour which would have hepatoprotective action, against the virus and at the same time enhance the protective action against hepatotoxic agents such as those in food, drug and alcohol.

The object of the present invention was therefore to provide for a synergistic composition having enhanced hepatoprotective action with reduced side effects.

Yet another object of the present invention is to provide for a composition having hepatoprotective effect against both viruses and hepatotoxic agents.

The aforesaid object is achieved by the present invention, which relates to a synergistic composition for the treatment of liver and liver associated ailments comprising:

extract of Glycyrrhiza glabra and Picrorhiza kurroa in ratio 2-1:1-3 by weight.

The said composition may be mixed with excipients for tableting.

The extracts of Glycyrrhiza glabra and Picrorhiza kurroa may be prepared in any known manner.

The extract of Glycyrrhiza Glabra may also be prepared after treating the powdered roots with a non polar solvent in the proportion of 1:5 by volume for removing unwanted components such as saponins, pigments and lipids in the supernatant. The residue obtained is mixed in 3-5 time volume of hot water at 60-90° C and constantly stirred for 3-5 hours. This water mixture is acidified and the residue extracted and dried in such a way that optimum concentration of Glycyrrhizin is obtained. The extract is standardized on TLC plates to obtain a definite number of components in each batch of the extract.

The extract of *Picrorhiza kurroa* may also be obtained after treatment of the dried powdered roots of the plants with petroleum ether in the proportion 1:3 by volume. The residue extracted with alcohol (60%) and left in cold water to remove / reduce the content of undesired components and concentrated to dryness to get optimized extract of *Picrorhiza kurroa*. The extract can be standardized by TLC to get same constituents in each batch of extract.

The composition of the herbal extracts in the present drug will enhance the hepatoprotective activity and at the same time reduce harmful side effects.

Method of Optimization

Optimization of Liquorice extract:

Glycyrrhizin content in liquorice root ranges from 3-6%. A standard curve is plotted of different UV readings taken from the after carrying out TLC test on of different conc. of pure Glycyrrhizin. The extract obtained from liquorice are put on TLC and the concentration of Glycyrrhizin in the extract is measured on UV and quantified with the help of the standard curve plotted above.

Optimization of Picrorhiza kurroa extract:

Similar procedure is carried out for optimizing the extract of *Picrorhiza kurroa* extract. Optimization is done to a stage of 40-70% content of Glycyrrhizin / Kutkin in the extracts.

The present invention will now be described with reference to foregoing examples:

Example 1:

The extract of *Glycyrrhiza glabra* is optimized at 50% Glycyrrhizin content. The extract of *Picrorhiza kurroa* is optimized at 40% kutkin content. 100mg of *Glycyrrhiza glabra* extract is mixed with 20mg of

Picrorhiza Kurroa extract to prepare the composition. Excipients are added to make a tablet form.

Example 2:

The extract of Glycyrrhiza glabra is optimized at 60% Glycyrrhizin content. The extract of Picrorhiza kurroa is optimized at 40% kutkin content. 84mg of Glycyrrhiza glabra extract is mixed with 31.5 of Picrorhiza Kurroa extract to prepare the composition. Excipients are added to make a tablet form.

DOSAGE:

Adult	-	2 Tablets Three times / day
Child	-	1 Tablet three times / day

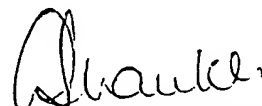
I claim:

1. A synergistic composition for the treatment of liver and liver associated ailments comprising:

extract of Glycyrrhiza glabra and Picrorhiza kurroa in ratio 2-1:1-3 by weight.

2. A composition as claimed in claim 1 wherein extract of Glycyrrhiza glabra is mixed with extract of Picrorhiza kurroa in the ratio of 1.25 : 2,
3. A synergistic composition for the treatment of the treatment of liver and liver associated ailments substantially as herein described with reference to the foregoing examples.

Dated this 21st day of July, 1999


Of Anand & Anand, Advocates
Agent for the Applicant

ABSTRACT

This invention relates to a synergistic composition for the treatment of liver and liver associated ailments comprising:

extract of Glycyrrhiza glabra and Picrorhiza kurroa in ratio 2-1:1-3 by weight.

REC'D	12 JAN 2000
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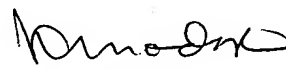
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THE PATENTS ACT, 1970

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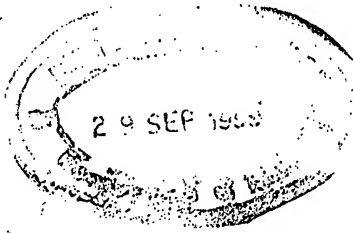
IT IS HEREBY CERTIFIED that annexed hereto is
a true copy of the Application form and Complete Patent
Specification in respect of Patent Application No.660/Cal/99
filed on 26th July, 1999 by RAJGARHIA, Ashok, C/o. Rajgarhia
Paper Mills Pvt. Ltd., 15, Exchange Place, Calcutta 700 001,
India,

Witness my hand: This the 25th day of October, 1999
This the 3rd day of Kartika 1921 (Saka)


(K. K. MODAK)

ASSTT. CONTROLIER OF PATENTS & DESIGNS.

The Patent Office,
Govt. of India,
2nd M.S.O. Building, 5th, 6th & 7th floor,
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Calcutta 700 020.



FORM 1
THE PATENTS ACT, 1970
(39 of 1970)
APPLICATION FOR GRANT OF A PATENT
(See Sections 5(2), 7, 54 and 135)

1. I/we,

(a) *RAJGARHIA, Ashok*

(b) *C/o Rajgarhia Paper Mills Pvt. Ltd., 15 Exchange Place, Calcutta - 700001, India.*

(c) *Indian*

2. hereby declare -

(a) that I am/we are in possession of an invention titled "*A Process For Preparing A Synergistic Composition For The Treatment Of Liver And Liver Associated Ailments.*"

(b) that the provisional-/ complete specification relating to this invention is filed with this application

(c) that there is no lawful ground of objection to the grant of a patent to me/us.

3. further declare that the inventor(s) for the said invention

4. I/we claim the priority from the application(s) filed in convention countries, particulars of which are as follows: *NIL*

5. I/we state that the said invention is an improvement in or modification of the invention the particulars of which are as follows and of which I/we are the applicant/patentee: *NIL*

6. I/we state that the application is divided out of my/our application, the particulars of which are given below and pray that this application be deemed to have been filed on _____ under section 16 of the Act. *NIL*

7. That I am/we are the assignee or legal representative of the true and first inventors

8. That my/our address for service in India is as follows:

*ANAND & ANAND, Advocates
B-41, Nizamuddin East
New Delhi - 110 013*




*Tel Nos.: (11) 4643078, 4643076, 4640360
Fax Nos.: (11) 4624243, 4642060*

9. Following declaration was given by the inventor(s) or applicant(s) in the convention country:

I/we the true and first inventors for this invention or the applicant(s) in the convention country declare that the applicant(s) herein is/are my/our assignee or legal representative

*RAJGARHIA, Ashok, C/o Rajgarhia Paper Mills Pvt. Ltd., 15 Exchange Place,
Calcutta - 700001, India, an Indian national.*


RAJGARHIA, Ashok

Date: 21st July, 1999

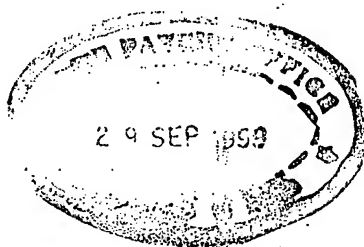
10. that to the best of my/our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to me/us on this application.
11. Followings are the attachment with the application:
- (a) provisional/-complete specification (3 copies)
 - (b) Abstract
 - (c) Power of Attorney
 - (d) Form 1 (in triplicate)
 - (e) Fee Rs. 1500.00 In cash/cheque/bank draft bearing no. _____, date _____ on _____ Bank.

I/we request that a patent may be granted to me/us for the said invention

Dated this 21st day of July, 1999

Ashok Rajgarhia
RAJGARHIA, Ashok

To
The Controller of Patents
The Patent Office,
Calcutta



THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

SECTION 10

*"A PROCESS FOR PREPARING A SYNERGISTIC
COMPOSITION FOR THE TREATMENT OF LIVER AND
LIVER ASSOCIATED AILMENTS"*

*Ashok Rajargaria, an Indian national of Rajargaria Paper
Mills Pvt. Limited, 15 Exchange Place, Calcutta 700001, West
Bengal, India*

The following specification particularly describes and ascertains
the nature of this invention and the manner in which it is to be
performed:

The present invention relates to a process for preparing a synergistic composition for the treatment of liver and liver associated ailments.

Background

Liver is an important organ in the human body and is responsible for its well being. It helps in detoxifying many exogenous toxic substances present within the human body, which are consumed as drugs or with food. These toxic wastes reduce the efficiency of the liver as a blood purifier. Liver also undergoes frequent attacks by viral infections such as hepatitis.

India has the second largest pool of HBV carriers in the world. It has a population of over 45 million HBV carriers and 15 million HCV carriers. One fourth of these are at risk to suffer from chronic liver diseases and its lethal complications, such as cirrhosis or even liver carcinoma. Coupled with the burden of HBV related liver diseases, there is an ever increasing patient load due to Hepatitis C. Screening of all the blood before use for HIV, is still a distant reality and this contributes to a significant increase in chronic liver diseases in India.

Therefore it has become absolutely essential to develop an effective therapeutic strategy to tackle this problem.

In allopathy, at present no specific drug is available for providing adequate cover for protection of or preventing liver from various infections and diseases. In Ayurveda, many plant extracts are known, which have a hepatoprotective effect. However, the effect of such crude plant extracts as used in Ayurveda is slow by virtue of presence of other components which may prevent full action of the active ingredient/component.

One of the plant extracts used as medicine for treatment of liver diseases is the root extract of plant *Glycyrrhiza glabra* (liquorice).

Said extract contains flavonoids, saponins, oligo-glycosides, phenolic compounds and glycyrrhizic acid. Glycyrrhiza glabra is known to have four actions which help in treatment and prevention of liver diseases (Sub acute liver failure, cirrhosis liver with activity)

Cyto-protective action - This helps in fortifying the cell, which enables the cell to protect itself from virus / infection.

Anti-inflammatory and Immunomodulatory action - This helps in reducing the inflammation of the organ and help modulate the organ to function normally. It also has cholerectic action.

Anti-oxidant action - Helps in preventing replication of virus.

Anti-viral action - The combined effect of the above helps in preventing replication of virus, thus there is reduction of viral load over a period of continued administration of the drug.

The activity of the extract of Glycyrrhiza glabra is also due to the action of beta glycyrrhizinic acid at the level of complement component C2.

However, liquorice extract when taken in large quantities for prolonged periods, causes high blood pressure (hypertension), water retention, weight gain due to pseudoaldosteronism and possibly heart complications.

Extract of roots of Picrorrhiza Kurroa have also been recommended as a hepatoprotective agent for protection of liver toxicity caused by hepatotoxic agents such as alcohol, carbon tetra chloride, viruses and parasites. Roots of Picrorrhiza kurroa contain glycosides, kutkin (kutkosides and

picrosides) and other organic acids such as vallanic and cinnamic acids.

The extract of Picrorrhiza roots is bitter and it increases gastric secretion, diminishes the force of heartbeat and reduces the blood pressure.

Therefore there was a need to develop a synergistic composition having a pleasant flavour which would have hepatoprotective action, against the virus and at the same time enhance the protective action against hepatotoxic agents such as those in food, drug and alcohol.

The object of the present invention was therefore to provide for a process for preparing a synergistic composition having enhanced hepatoprotective action with reduced side effects.

Yet another object of the present invention is to provide for a composition having hepatoprotective effect against both viruses and hepatotoxic agents.

The aforesaid object is achieved by the present invention, which relates to a process for preparing a synergistic composition for the treatment of liver and liver associated ailments comprising:

- preparation of extract from the roots of Glycyrrhiza Glabra and Picrorrhiza kurroa.
- optimization of the extract of Glycyrrhiza glabra to ensure the maximum content of glycyrrhizin.
- optimization of the extract of Picrorrhiza kurroa to ensure maximum content of Kutkin.
- mixing the two extracts obtained in ratio 2-1:1-3 at ambient temperature and pressure to obtain the composition.

The said composition may be mixed with excipients for tableting.

The extracts of Glycyrrhiza glabra and Picrorhiza kurroa may be prepared in any known manner.

The extract of Glycyrrhiza Glabra may also be prepared after treating the powdered roots with a non polar solvent in the proportion of 1:5 by volume for removing unwanted components such as saponins, pigments and lipids in the supernatant. The residue obtained is mixed in 3-5 time volume of hot water at 60-90° C and constantly stirred for 3-5 hours. This water mixture is acidified and the residue extracted and dried in such a way that optimum concentration of Glycyrrhizin is obtained. The extract is standardized on TLC plates to obtain a definite number of components in each batch of the extract.

The extract of Picrorhiza kurroa may also be obtained after treatment of the dried powdered roots of the plants with petroleum ether in the proportion 1:3 by volume. The residue extracted with alcohol (60%) and left in cold water to remove / reduce the content of undesired components and concentrated to dryness to get optimized extract of Picrorhiza kurroa. The extract can be standardized by TLC to get same constituents in each batch of extract.

The composition of the herbal extracts in the present drug will enhance the hepatoprotective activity and at the same time reduce harmful side effects.

Method of Optimization

Optimization of Liquorice extract:

Glycyrrhizin content in liquorice root ranges from 3-6%. A standard curve is plotted of different UV readings taken from the after carrying out TLC test on of different conc. of pure

Glycyrrhizin. The extract obtained from liquorice are put on TLC and the concentration of Glycyrrhizin in the extract is measured on UV and quantified with the help of the standard curve plotted above.

Optimization of Picrorhiza kurroa extract:

Similar procedure is carried out for optimizing the extract of Picrorhiza kurroa extract. Optimization is done to a stage of 40-70% content of Glycyrrhizin / Kutkin in the extracts.

The present invention will now be described with reference to foregoing examples:

Example 1:

The extract of Glycyrrhiza glabra is optimized at 50% Glycyrrhizin content. The extract of Picrorhiza kurroa is optimized at 40% kutkin content. 100mg of Glycyrrhiza Glabra Extract is mixed with 20mg of Picrorhiza kurroa extract to prepare the composition. Excipients are added to make a tablet form.

Example 2:

The extract of Glycyrrhiza glabra is optimized at 60% Glycyrrhizin content. The extract of Picrorhiza kurroa is optimized at 40% kutkin content. 84mg of Glycyrrhiza Glabra Extract is mixed with 31.5 of Picrorhiza kurroa extract to prepare the composition. Excipients are added to make a tablet form.

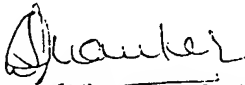
DOSAGE:

Adults	-	2 Tablets three times / day
Child	-	1 Tablet three times / day

I claim:

1. A process for preparing a synergistic composition for the treatment of liver and liver associated ailments comprising:
 - preparation of extract from the roots of Glycyrrhizia Glabra and ~~Picrorhiza kurroa~~.
 - optimization of the extract of Glycyrrhiza glabra to ensure the maximum content of glycyrrhizin.
 - optimization of the extract of Picrorhiza kurroa to ensure maximum content of Kutkin.
 - mixing the two extracts obtained in ratio 2-1:1-3 at ambient temperature and pressure to obtain the composition.
2. A process as claimed in claim 1 wherein extract of Glycyrrhiza glabra is mixed with extract of Picrorhiza kurroa in the ration 1:25 : 2.
3. A process for preparing a synergistic composition for the treatment of the treatment of liver and liver associated ailments substantially as herein described with reference to the foregoing examples.

Dated this 21st day of July, 1999


Of Anand & Anand, Advocates
Agent for the Applicant

ABSTRACT

This invention relates to a process for preparing a synergistic composition for the treatment of liver and liver associated ailments comprising:

- preparation of extract from the roots of Glycyrrhizia Glabra and Picrorhiza kurroa.
- optimization of the extract of Glycyrrhiza glabra to ensure the maximum content of glycyrrhizin.
- optimization of the extract of Picrorhiza kurroa to ensure maximum content of Kutkin.
- mixing the two extracts obtained in ratio 2-1:1-3 at ambient temperature and pressure to obtain the composition.